International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 7, No. 1, 2024

The Impact and Mechanism of Arabinoxylan on Behavioral Regulation in PSD Rats via Gut Microbiota Modulation

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Abstract: Objective To investigate the mechanism by which arabinoxylan modulates gut microbiota and promotes neuronal function recovery in post-stroke depression (PSD) rats. Methods The PSD rat model was established using the middle cerebral artery occlusion (MCAO) method combined with chronic unpredictable mild stress (CUMS). Behavioral changes were observed, and 16S rDNA sequencing was used to analyze gut microbiome alterations. Enzyme-linked immunosorbent assay (ELISA) was conducted to measure serum levels of serotonin (5-HT), norepinephrine (NE), and dopamine (DA). Reverse transcription polymerase chain reaction (RT-PCR) was used to detect the expression of brain-derived neurotrophic factor (BDNF) mRNA in the frontal cortex. Results Arabinoxylan significantly increased activity levels in PSD rats, enriched the diversity of gut microbiota, elevated the levels of monoamine neurotransmitters (5-HT, NE, and DA), and upregulated the expression of BDNF mRNA in the frontal cortex. Conclusion Arabinoxylan ameliorates depressive-like behavior in PSD rats, enhances gut microbiota diversity, potentially upregulates the expression of monoamine neurotransmitters (5-HT, NE, and DA) via the microbiota-gut-brain axis, and increases BDNF mRNA levels in the frontal cortex, thereby promoting neuronal function recovery.

Keywords: Post-Stroke Depression; Arabinoxylan; Gut Microbiota; Behavior; Monoamine Neurotransmitters.

1. Introduction

Post-stroke depression (PSD) is a common emotional disorder complication that has garnered increasing attention in recent years due to its rising incidence. PSD is characterized by symptoms such as low mood, loss of interest, and even suicidal ideation and behaviors [1]. The etiology of PSD is complex, with the neurochemical hypothesis and the microbiota-gut-brain axis theory gaining growing acceptance. Serotonin (5-hydroxytryptamine, 5-HT), dopamine (DA), and norepinephrine (NE) are important monoamine neurotransmitters that transmit excitatory signals through neuronal axons to the thalamus, basal ganglia, and frontal cortex, playing a role in emotional regulation. Disruption of these neural pathways can lead to decreased neurotransmitter expression, resulting in depression [2]. Brain-derived neurotrophic factor (BDNF) plays a crucial role in the development and function of the nervous system [3]. BDNF expression affects neuronal growth, differentiation, synaptic plasticity, and the repair of damaged neurons [4]. Clinical studies have shown that BDNF expression in the brain is reduced in PSD patients [5]. With the advancement of gut metagenomics, more researchers are exploring the relationship between the microbiota-gut-brain axis and neurological diseases, finding that gut microbiota can influence PSD occurrence and progression through metabolic, immune, endocrine, and neuroendocrine pathways [6]. Currently, fluoxetine (FLX), a commonly used selective serotonin reuptake inhibitor, can increase brain BDNF levels and alleviate depressive symptoms, but long-term use of antidepressants is associated with various side effects [7]. Prebiotics, probiotics, and gut metabolites such as short-chain fatty acids can increase brain BDNF expression and improve depressive symptoms [8,9]. Arabinoxylan (AX) is a natural gut microbiota regulator recognized as a novel prebiotic with the ability to modulate gut microbiota [10]. Previous research by our team found that arabinoxylan combined with Madopar could improve behavioral symptoms, gut microbiota structure, and the function of nigral dopaminergic neurons in Parkinson's disease rats through the microbiota-gut-brain axis [11]. However, research on arabinoxylan for PSD treatment is limited. This study aims to explore how arabinoxylan modulates gut microbiota to exert neuroprotective effects and improve PSD symptoms through the microbiota-gut-brain axis. This research provides a basis for further understanding the antidepressant mechanism of arabinoxylan and offers theoretical support for developing prebiotics as new drugs for PSD treatment.

2. Materials

2.1. Experimental Animals

Thirty male Sprague-Dawley rats, weighing 180-200g and aged 7-8 weeks, were obtained from Guangdong Viton Lihua Laboratory Animal Technology Co., Ltd. The certification number for the animal experimental facility is SYXK Gui 2022-0004, and the quality certificate number is 44829700014301. The rats were kept at a room temperature of (24±2) °C with a light cycle from 8:00 to 20:00, and a relative humidity of (50±5) %. They had free access to food and water. The rats were acclimatized and housed in separate cages in an SPF-level quarantine room for at least one week before being transferred to the SPF-level experimental room, ensuring no pathogenic conditions were present. Rats weighing between 240-260g were selected for model construction. The experimental design was approved by the Ethics Committee of the Science and Technology Department of Youjiang Medical University for Nationalities (Approval No.: 2023060902).

2.2. Drugs and Reagents

Isoflurane (Tianjin Ruipu Biotechnology Co., Ltd., 20037015); Arabinoxylan (Shanghai Septer Molecular Biotechnology Co., Ltd., SEP20210506A01); Fluoxetine capsules (Shanxi Qianyuan Pharmaceutical Group Co., Ltd., 220404); 5-HT ELISA kit (E-EL-0033); NE ELISA kit (E-EL-0047); DA ELISA kit (E-EL-0046), all purchased from Wuhan Elabscience Biotechnology Co., Ltd.; SYBR QPCR master mix (22208-01) and All-in-one RT Easy Mix for qPCR (22107), both purchased from Shanghai Tolo Biotech Co., Ltd.

2.3. Instruments

Small animal anesthesia machine (Shanghai Ta Wang Intelligent Technology Co., Ltd.); Open field test video analysis system (Guangzhou Hanchen Experimental Equipment Co., Ltd.); Electrophoresis apparatus (Bio-Rad, DYY-6C); VICTOR Nivo multifunctional microplate reader (PerkinElmer, USA); PCR amplification instrument (Thermo Fisher Scientific); High-throughput sequencer (Illumina Miseq2000).

3. Methods

3.1. Preparation of PSD Model

The model was established using the middle cerebral artery occlusion (MCAO) method combined with chronic unpredictable mild stress (CUMS). SD rats were deeply anesthetized using a small animal anesthesia machine. The neck muscles, nerves, and blood vessels were gradually separated. A filament was inserted into the right internal carotid artery and advanced 1.8-2.0 cm to reach the middle cerebral artery. The filament was left in place for 2 hours and then slowly removed. On the 7th day after the successful establishment of the cerebral ischemia model, the rats were individually housed and subjected to chronic unpredictable mild stress to induce the PSD model. The stressors included: 1) 24-hour food deprivation; 2) 24-hour water deprivation; 3) 45° cage tilt for 24 hours; 4) 6-hour restraint in a tube; 5) 24-hour light-dark cycle reversal; 6) 1-minute tail pinch; 7) 24-hour wet bedding. Different stressors were randomly given daily for 21 days.

3.2. Neurological Motor Function Scoring of Rats

Two hours after the rats awoke, neurological function was scored according to the Longa scoring criteria, and the filament was removed.

3.3. Animal Grouping and Drug Administration

Rats weighing 240-260g were included in the study, with a total of 30 rats. They were randomly assigned to a blank control group and an MCAO surgery group based on their weight. The surgery group underwent MCAO modeling, and surviving rats were selected 7 days later for the experiment. According to the random number table, rats were further divided into the post-stroke depression group, arabinoxylan group, fluoxetine hydrochloride group, and the combined fluoxetine hydrochloride and arabinoxylan group. Except for the 6 rats in the blank control group, which were housed together, the other groups were individually housed. After 21 days of CUMS stress, drug intervention was started for 28 days. The rats were gavaged once daily, with the dosage adjusted according to weight changes. The blank control group and post-stroke depression group received 10 mg/kg of distilled water; the arabinoxylan group received 800 mg/kg arabinoxylan dissolved in distilled water; the fluoxetine hydrochloride group received a 5 mg/kg suspension.

3.4. Behavioral Measurement

Open Field Test (OFT)

Before the experiment, ensure a quiet environment. Place the rat individually in a novel open-field box (80 cm × 80 cm × 60 cm) and allow it to explore freely for 5 minutes. An automatic video tracking system records the activity for 5 minutes.

3.5. 16s rDNA Gene Sequencing of Rat Gut Microbiota

Genomic DNA of fecal samples was extracted using a magnetic bead method, followed by library construction, library quantification, normalization, mixing, high-throughput sequencing, and data analysis to obtain metagenomic changes in the rat gut microbiota.

3.6. ELISA (Enzyme-Linked Immunosorbent Assay) Detection of Serum Monoamine Neurotransmitter Levels in Rats

3.6.1. Sample Preparation

Rats were deeply anesthetized, decapitated, and the brain was placed on ice. The prefrontal cortex was dissected. Blood samples were left to stand at room temperature for half an hour, then centrifuged at 1500 × g for 10 minutes to collect the supernatant for detection. Prefrontal cortex samples were washed with pre-cooled PBS (0.01M, pH=7.4), weighed, minced, added to PBS with protease inhibitors, and homogenized. Finally, the homogenate was centrifuged at 5000 × g for 15 minutes at low temperature, and the supernatant was collected for detection.

3.6.2. ELISA Detection

Add the supernatant to the wells, seal the plate, and incubate at 37 ℃ for 45 minutes. Wash the plate 3 times, add HRP-conjugate, seal the plate, and incubate at 37 ℃ for 30 minutes. Wash the plate 5 times, add substrate solution (TMB), seal the plate, and incubate at 37 ℃ for 15 minutes to develop the color. Finally, add stop solution to terminate the reaction. Measure absorbance at 450 nm using a microplate reader within 10 minutes, plot the standard curve, and calculate the content of the samples.

3.7. Reverse Transcription-Polymerase Chain Reaction (RT-PCR) Detection of BDNF mRNA Expression in the Prefrontal Cortex

Prefrontal cortex tissue was lysed with Trizol reagent, total RNA was extracted, reverse transcribed into cDNA, and amplified by PCR. The PCR reaction was performed according to the kit instructions, with β-actin as the internal reference. The relative expression level of BDNF mRNA was calculated using the 2-ΔΔCt method.

3.8. Statistical Analysis

Statistical analyses were performed using SPSS 27.0 and GraphPad v10 software. Normality of the data was assessed using the Shapiro-Wilk test, and homogeneity of variance was evaluated using Levene's test. Measurement data are

described as mean ± standard deviation (SD). Comparisons between groups were conducted using one-way analysis of variance (ANOVA). If variances were equal, Tukey's multiple comparison test was used; if variances were unequal, Tamhane's T2 test was applied. A significance level of $P < 0.05$ was considered statistically significant.

4. Results

4.1. Effect of AX on Locomotor Activity in PSD Rats in the Open Field Test

The movement trajectory of the rats was used to reflect their interest in exploring a novel environment. The activity level in the open field test was used to assess the locomotor activity of the rats, with higher activity levels indicating less depression. After 28 days of AX administration, compared to the CON group (9.01±1.03), the activity level of the PSD group (6.19±0.28) significantly decreased, with a statistically significant difference ($P < 0.01$). Compared to the PSD group, the activity level of the AX group (7.27±0.31) significantly increased, with a statistically significant difference ($P < 0.05$). Compared to the AX group, the activity level of the FLX group (8.39±0.33) significantly increased, with a statistically significant difference ($P < 0.05$). Compared to the FLX group, the activity level of the FLX+AX group (9.49±0.44) significantly increased, with a statistically significant difference ($P < 0.05$). The use of a placebo did not significantly change the activity levels of the CON and PSD groups, with no statistically significant difference ($P > 0.05$) (see Figure 1).

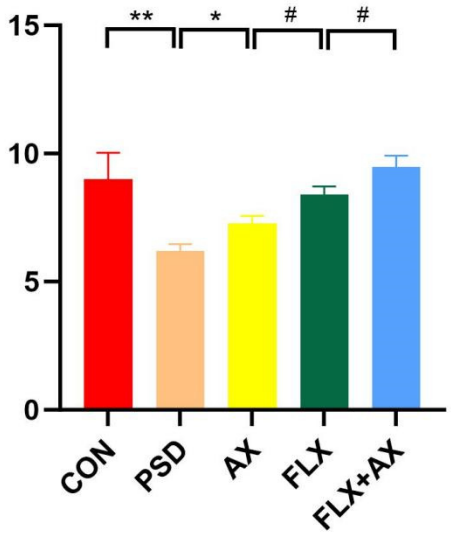

Figure 1. Activity Levels of Rats in the Open Field Test
*Note: Compared to the PSD group, *P < 0.05, *P < 0.01; compared to the FLX group, #P < 0.05.

4.2. Effect of AX on Serum Neurotransmitter Levels

4.2.1. Effect of AX on Serum 5-HT Levels

Serum 5-HT levels in each group of rats were measured, showing that compared to the CON group (160.34±29.96 ng/ml), the PSD group (70.34±24.83 ng/ml) significantly decreased, with a statistically significant difference ($P < 0.01$). Compared to the PSD group, the AX group (128.75±19.04 ng/ml) significantly increased, with a statistically significant difference ($P < 0.05$). Compared to the AX group, the FLX group (152.75±20.98 ng/ml) showed no statistically significant difference ($P > 0.05$). Compared to the FLX group, the FLX+AX group (219.81±55.83 ng/ml) significantly increased, with a statistically significant difference ($P < 0.05$) (see Figure 2).

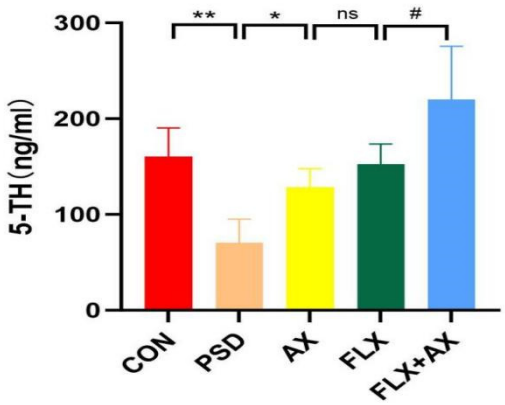

Figure 2. Serum 5-HT Levels in Each Group of Rats
*Note: Compared to the PSD group, *P < 0.05, *P < 0.01; compared to the FLX group, #P < 0.05.

4.2.2. Effect of AX on Serum DA Levels

Serum DA levels in each group of rats were measured, showing that compared to the CON group (471.95±57.36 ng/ml), the PSD group (113.94±31.98 ng/ml) significantly decreased, with a statistically significant difference ($P < 0.01$). Compared to the PSD group, the AX group (193.84±43.69 ng/ml) significantly increased, with a statistically significant difference ($P < 0.01$). Compared to the AX group, the FLX group (276.12±33.53 ng/ml) significantly increased, with a statistically significant difference ($P < 0.05$). Compared to the FLX group, the FLX+AX group (438.5±36.55 ng/ml) significantly increased, with a statistically significant difference ($P < 0.05$) (see Figure 3).

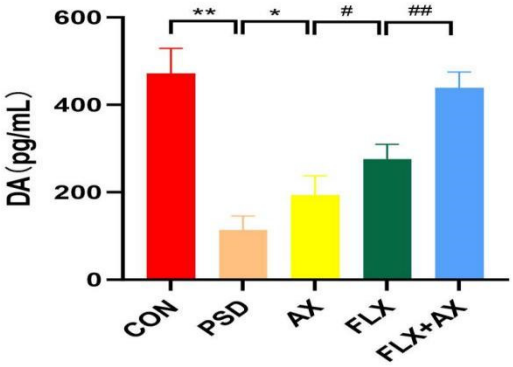

Figure 3. Serum DA Levels in Each Group of Rats
*Note: Compared to the PSD group, *P < 0.05, *P < 0.01; compared to the FLX group, #P < 0.05, ##P < 0.01.

4.2.3. Effect of AX on Serum NE Levels

Serum NE levels in each group of rats were measured, showing that compared to the CON group (18.26±2.55 ng/ml), the PSD group (2.21±0.32 ng/ml) significantly decreased, with a statistically significant difference ($P < 0.01$). Compared to the PSD group, the AX group (9.87±2.16 ng/ml) significantly increased, with a statistically significant difference ($P < 0.05$). Compared to the AX group, the FLX group (13.24±1.21 ng/ml) significantly increased, with a statistically significant difference ($P < 0.01$). Compared to the FLX group, the FLX+AX group (16.70±1.60 ng/ml) increased, with a statistically significant difference ($P < 0.05$) (see Figure 4).

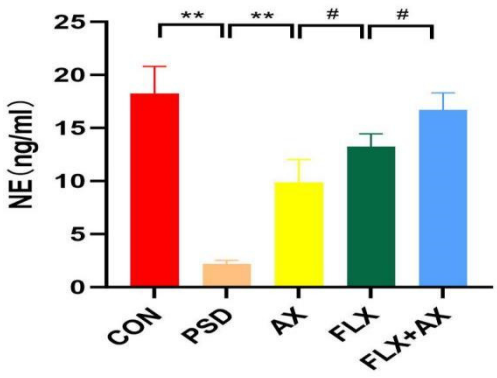

Figure 4. Serum NE Levels in Each Group of Rats
*Note: Compared to the PSD group, *P < 0.01; compared to the FLX group, #P < 0.05.

4.3. Effect of AX on Frontal Cortex BDNF mRNA Expression Levels

After 28 days of AX administration, compared to the CON group (1.00±0.03 pg/ml), the PSD group (0.42±0.03 pg/ml) showed a significant decrease in BDNF mRNA expression levels, with a statistically significant difference (P < 0.01). Compared to the PSD group, the AX group (0.63±0.04 pg/ml) showed a significant increase in BDNF mRNA expression levels, with a statistically significant difference (P < 0.05). Compared to the AX group, the FLX group (0.83±0.15 pg/ml) showed no statistically significant difference (P > 0.05). Compared to the FLX group, the FLX+AX group (1.02±0.08 pg/ml) showed no statistically significant difference (P > 0.05) (see Figure 5).

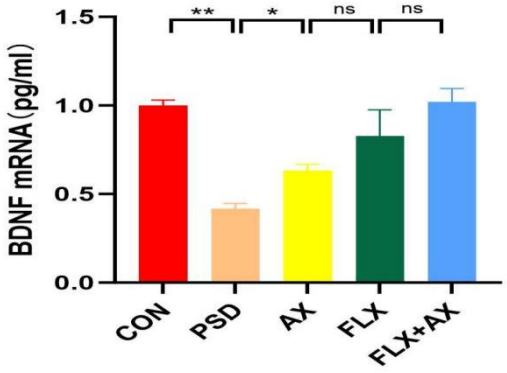

Figure 5. BDNF mRNA Expression Levels in the Frontal Cortex of Each Group of Rats
*Note: Compared to the PSD group, *P < 0.05, *P < 0.01.

4.4. Effect of AX on Intestinal Microbiota in Rats

4.4.1. Overall Composition and Differences in Intestinal Microbiota in Each Group of PSD Rats

High-throughput sequencing of the V3-V4 variable region of the 16S rDNA gene was performed on the feces of three groups of rats. The results showed differences in the amplified sequence variants (ASVs) among each group. The number of shared ASVs among the three groups was 209, with 175 unique ASVs in the CON group, 98 unique ASVs in the PSD group, and 130 unique ASVs in the AX group (see Figure 6).

Figure 6. Composition and Differences in Intestinal Microbiota of Each Group of Rats
Note: Each circle represents a group of samples. The numbers in the overlapping areas represent the shared ASVs among the samples, and the numbers in the non-overlapping areas represent the unique ASVs in the samples.

4.4.2. Changes in Intestinal Microbiota Diversity in Each Group of Rats

Principal component analysis (PCA) was conducted on the relative abundance data of different gut microbiota groups in the three groups, resulting in the changes in microbial beta diversity. The results showed that the CON group, PSD group, and AX group were spatially distant from each other, and the samples between the groups could be significantly distinguished from both the first and second principal components (see Figure 7).

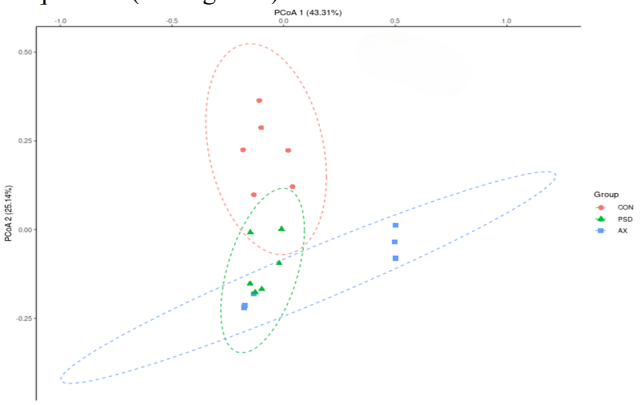

Figure 7. Microbial Diversity of Intestinal Microbiota in Each Group of Rats
*Note: Each point represents a sample, and the closer the points, the higher the similarity. The X-axis and Y-axis represent the first and second principal components, respectively.

4.4.3. Analysis of Species Differences in Intestinal Microbiota among Groups of Rats

The differential analysis of species among the three groups of intestinal microbiota showed that the genera Ruminococcaceae UCG-011 and Holdemania had the most significant differences between the groups (see Figure 8).

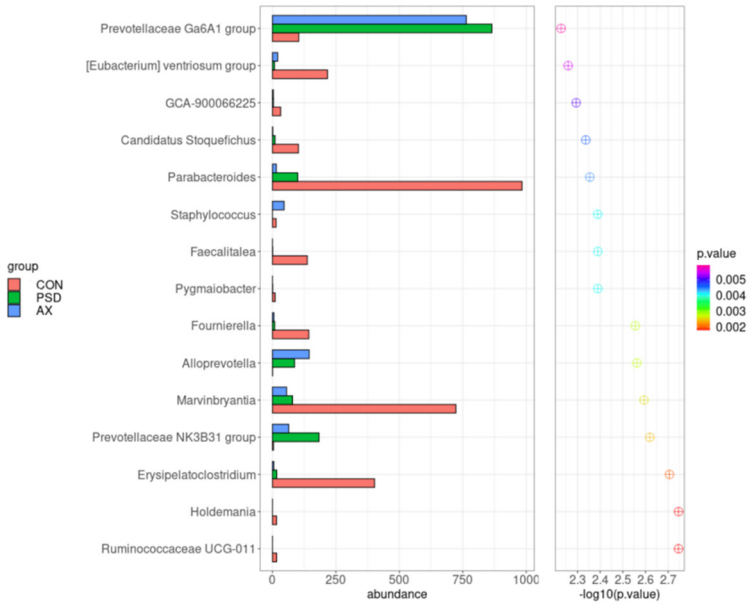

Figure 8. Species Differences in Intestinal Microbiota among Groups of Rats

*Note: The left figure shows the abundance of species with significant differences between the groups, with each bar representing the mean of the significantly different species in each group. The right figure shows the confidence intervals of the differences between the groups, with the leftmost point of each circle representing the lower limit of the 95% confidence interval of the mean difference, the rightmost point of the circle representing the upper limit of the 95% confidence interval of the mean difference, and the center of the circle representing the mean difference. The color of the circle represents the group with the higher mean. The far right shows the p-values for the significance tests of the differences between the groups for the corresponding species.

4.4.4. Correlation Analysis between Gut Microbiota and Serum 5-HT Levels

Correlation analysis of intestinal microbiota species among the three groups showed that the genera Erysipelotrichaceae UCG-003, Helicobacter, and Ruminococcaceae UCG-013 were significantly positively correlated with the group classification; the genus Erysipelatoclostridium was significantly positively correlated with serum 5-HT levels (see Figure 9).

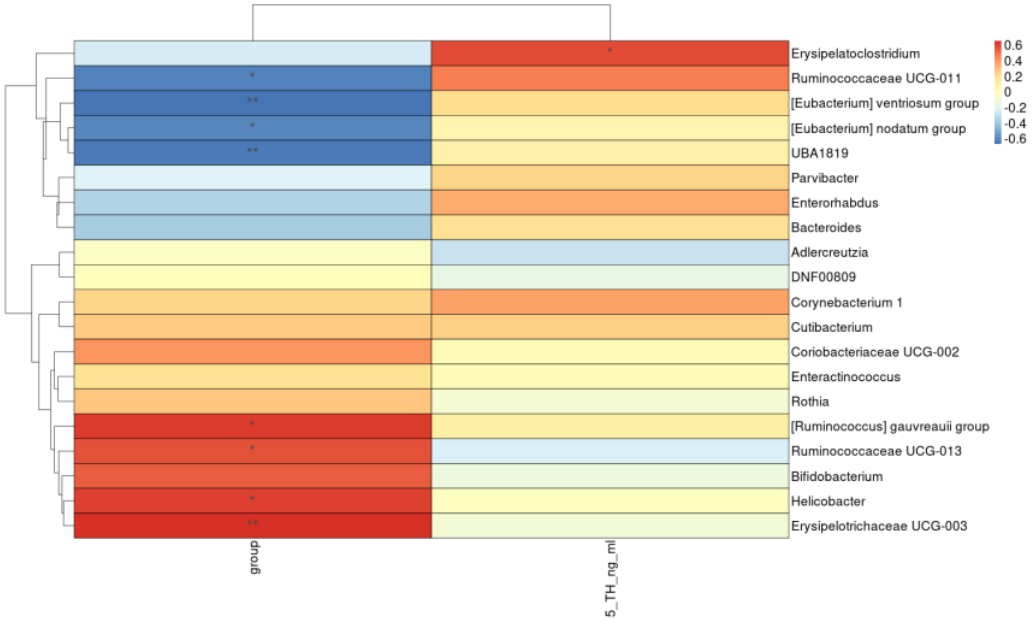

Figure 9. Correlation Analysis between Gut Microbiota and Serum 5-HT Levels

Note: The bottom labels indicate sample information, the right labels indicate species information, and the values in the middle heatmap correspond to the Spearman correlation coefficient r, ranging between -1 and 1, with r < 0 indicating a negative correlation and r > 0 indicating a positive correlation. An asterisk () denotes a significance test with P < 0.05.

5. Discussion

Post-stroke depression (PSD) is an emotional disorder syndrome occurring after a stroke, characterized primarily by low mood and loss of interest. PSD patients exhibit cognitive and fall impairments, poor prognosis, and suicide risk, posing a serious burden to society [12]. Depression can occur when monoamine neurotransmitters 5-HT, DA, and NE decrease [13]. Reduced levels of 5-HT, NE, and DA can exacerbate depressive symptoms, and currently, these can be used as important indicators for diagnosing depression [14]. Fluoxetine, widely used clinically, is a representative selective serotonin reuptake inhibitor for treating depression, but it also has many adverse reactions [15]. Recent research on the microbiota-gut-brain axis and its relation to PSD has found that supplementing with probiotics can prevent or treat neurological and psychiatric disorders such as depression [16-18]. Metagenomic sequencing of feces revealed that arabinoxylan increases the diversity of gut microbiota. Detection of serum 5-HT, DA, and NE showed that arabinoxylan significantly increases the expression of 5-HT, DA, and NE, alleviating depressive-like behaviors in PSD rats.

BDNF, an important biomarker for depression, promotes neuronal cell growth [19]. BDNF is a crucial neuromodulator for synaptic transmission and long-term potentiation in the brain, playing an important role in maintaining neuronal function, promoting neuronal regeneration, and inhibiting neuronal apoptosis [20,21]. In summary, arabinoxylan intake can improve depressive-like behaviors in PSD rats, enrich the diversity of gut microbiota, possibly upregulate the expression of monoamine neurotransmitters 5-HT, DA, and NE through the microbiota-gut-brain axis, and increase BDNF mRNA expression levels in the frontal cortex, thereby exerting an antidepressant effect.

Acknowledgments

This research was supported by the Guangxi Medical and Health Appropriate Technology Development and Promotion Application Program (S2018073) and the Youjiang Medical University for Nationalities Horizontal Project (YYHX 2021 001).

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